UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/748,739	12/26/2000	Oksana Lockridge	P-IX 4143	4261

23601 7590 11/10/2003

CAMPBELL & FLORES LLP
4370 LA JOLLA VILLAGE DRIVE
7TH FLOOR
SAN DIEGO, CA 92122

EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	19

DATE MAILED: 11/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

Office Action Summary	Appli ation No. 09/748,739	Applicant(s) LOCKRIDGE ET AL.	
	Examiner Bennett Celsa	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *3-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

Applicant's amendment dated 8/4/03 in paper no. 17 is acknowledged.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

DETAILED ACTION

Status of the Claims

Claims 1-39 are currently pending.

Claims 1-2 are under consideration to the extent they read on the elected invention.

Claims 3-39 are withdrawn from consideration as being directed to a nonelected invention.

Election/Restriction

1. Applicant's election with traverse of Group I (claims 1-2, in part, drawn to a peptide comprising substantially the same amino acid sequence as seq. Id 2) in Paper No. 10 is again acknowledged. The traversal is on the ground(s) that restricting between a peptide comprising substantially sequence of a given peptide sequence AND a peptide comprising substantially the same sequence of a functional fragment of a sequence (e.g. Group I and II) is not proper since the search is not burdensome e.g. a search of group I will uncover art relevant to group II and group I and II are classified similarly, . This is not found persuasive for the reasons provided in the Restriction/Election e.g. the fragment will require different and separately burdensome, manual and computer sequence and bibliographic searches. Additionally, contrary

to applicant's argument, and as discussed in the restriction/election requirement, the fragment, will be classifiable in different subclasses as compared to the entire sequence. .

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 3-39 drawn to a nonelected invention. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Withdrawn Objection (s) and/or Rejection (s)

Applicant's amendment has overcome the anticipation rejection of claims 1-2 over Broomfield et al. US Pat. No. 6,001,625 (12/99) or Sevigny et al. WO 99/66072 (12/23/99).

Applicant's amendment has overcome the double patenting rejection of claims 1-2 over Broomfield et al. US Pat. No. 6,001,625 (12/99).

Outstanding Objection (s) and/or Rejection (s)

Claim Rej ctions - 35 USC § 112

2. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (LACK OF WRITTEN DESCRIPTION).

Claims 1 and 2, encompass peptide"butyrylcholinesterase variants" (e.g see specification pages 7-11; 16-17) having a tryptophan as an amino acid at position 328 and which are "substantially the same" as seq. 2: (e.g. a peptide of 602 amino acids) which include peptide sequences identical to seq. 2 as well as any other peptide having **one or more amino** acid changes (deletions, additions, substitutions or any other alteration etc.); such alterations employing not only the 20 naturally occurring amino acids but the corresponding 20 D-amino acids as well as "amino acid analogues" and "amino acid mimetics" as long as the resulting "variant" is "substantially the same" e.g. exhibits cocaine hydrolysis activity ((increased/decreased/same) and is the same or has "a similar , nonidentical sequence that is considered by those skilled in the art to be a functionally equivalent amino acid sequence". Although the specification recites that a "variant" can have "at least 70% (or more)" sequence identity, the claims are not so limited. Accordingly, the parameters to be followed by a skilled artisan to determine "functional equivalence" are not circumscribed by either the specification or the claims. Additionally, the term "mimetic" and "analog" is not defined by the specification and the degree of structure and/or functional properties that constitute an "amino acid mimetic(analogue)" (relative to a given standard amino acid) is not defined nor is the means and conditions of measurement. Further, the term "substantially the same

amino acid sequence" is a relative term which renders the claim indefinite since this term is not precisely defined by the claim, nor does the specification provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Accordingly, the term "butyrlcholinesterase variant" is equally "relative" and indefinite. Even specifying that the "variant" possess "a 15-fold increase in hydrolysis activity" does not render claim 1 definite for the following reasons. Additionally, the definition of "butylcholinesterase" encompasses any native mammalian butylcholinesterase and "isotype variation, polymorphism or any other allelic variation(s) " thereof . Accordingly, there is NO specific butylcholinesterase standard for measuring increased hydrolysis activity. Secondly, specifying hydrolysis activity does not address the structural lack of metes and bounds regarding the term "variant" as discussed above.

Thus, the claimed invention encompasses billions of potential deletion/substitution/addition or other alteration variants derivable from of the 602 amino acid protein of seq. Id 2, using only the 20 natural amino acids and the 20 corresponding D-amino acids as monomers [e.g. without use of "amino acid analogs (or mimetics)]. These variants need not share any decipherable common peptide core structure but merely must contain tryptophan as an amino acid at position 328.

In support of the claimed "butylcholinesterase variants" of such diverse sequence structure, the specification provides four (4) butyrcholineterase variants of identical peptide length each of which has only one variation e.g. a single natural amino acid substitution; which includes a single amino acid variant .

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

Although directed to DNA compounds, this holding would be deemed to be applicable to a generic of compounds; which requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the compound or generic(s). For example, in a recent court case in line with *Eli Lilly, Judge Lourie writing for the CAFC* made the following observation:

"A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) having the function of lessening inflammation of tissues, fails to distinguish any steroid from others having the same activity or function. Similarly, the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity. "

See: J. Lourie decision in *Enzo Biochem, Inc. v. Gen-Probe Inc. et al.* No. 01-1230 (CAFC: Decided April 2, 2002) (citation forthcoming).

In this regard, applicant is referred to the seminal case of *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and the "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001).

It is noted that **written description is legally distinct from enablement**: "Although the two concepts of are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures the that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co.*

As pointed out above, the specification discloses only limited examples that are neither representative of the claimed "butyrcholinesterase variants"; nor do 4 species represent a substantial portion of the claimed genus sufficient to satisfy the description requirement

Discussion

Applicant's amendment and arguments directed to the above rejection were considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above rejection was modified in response to applicant's amendment.

Applicant cites various case law (e.g. *Moba v. Diamond Automation; Enzo Biochem, Inc. v Gen-Probe, Inc.*") and appears to argue that the written description requirement is satisfied if a particular chemical structure sufficiently correlates to a

particular function. In this regard applicant argues (citing specification page 22 e.g lines 17-28) that the specification teaches an A328W butylcholineesterase variant (e.g. a tryp or W substitution for ala or A) obtained from PCR cite-directed mutagenesis of human butrylcholinesterase which has "at least a 15 fold increase in cocaine hydrolysis activity compared to human butyrlcholinesterase" (as described in Example 1). Applicant then argues that "The disclosed function of at least a fifteen-fold increase in cocaine hydrolysis activity compared to human butrylcholinesterase is sufficiently correlated to a particular known structure , in particular the change at amino acid position 328 of human butyrlcholinesterase (SEQ ID No. 17). Applicant further argues that the specification provides written description of "substantially similar sequence" that "have an identical amino acid sequence, or a similar, non-identical sequence that is considered by those skilled in the art to be a functionally equivalent amino acid sequence and is at least 70% identical in sequence to the reference butyrlcholinesterase".

Applicant's arguments and amendment were considered but deemed nonpersuasive for the reasons provided in the above rejection and for the following reasons.

Initially, it is noted that applicant's arguments are not commensurate to the claimed invention which is not limited to any particular amount of percent identity.

Additionally, a single butyrcholinesterase variant A328W does not provide support for a "generic" which reads on billions of addtion/substitution/deletion variants which but for having tryptophan at position 328 would contain no common peptide core

structure. Neither Applicant's specification, nor applicant's claims provides the requisite additional amino acid peptide core structure, in addition to W at position 328, which is needed to obtain functional butyrlcholinesterase variants (e.g. 15 fold increase in cocaine hydrolysis activity) as presently claimed. Nor do applicant's specification/claims provide a representative sample of A328W butyclolinesterase variant peptides, in addition to 328W to, necessary to demonstrate possession of the broad "generic" (which lacks the necessary core structure) of variants. In this regard it is noted that in the specification (e.g. Table 4) changes of a single amino acid position resulted in many INACTIVE butyrlcholinesterase variants; and those variants not inactive, were nevertheless poor binders (e.g. >> 1 micromolar binding/cocaine hydrolysis).

Accordingly, the above written description rejection is hereby maintained.

3. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 2, the "butyrylcholinesterase variants" and "substantially the same" and their corresponding specification definitions lack particularity and metes and bounds and are thus indefinite. The term "butyrylcholinesterase variants" (e.g see specification pages 7-11; 16-17) encompass peptides that are "substantially the same" as seq. 2: (e.g. a peptide of 602 amino acids) which include peptide sequences identical to seq. 2 as well as any other peptide having **on or m r amino** acid changes (deletions, additions, substitutions or any other alteration etc.); such alterations

employing not only the 20 naturally occurring amino acids but the corresponding 20 D-amino acids as well as "amino acid analogues" and "amino acid mimetics" as long as the resulting "variant" is "substantially the same" e.g. exhibits cocaine hydrolysis activity ((increased/decreased/same) and is the same or has "a similar , nonidentical sequence that is considered by those skilled in the art to be a functionally equivalent amino acid sequence". Although the specification recites that a "variant" can have "at least 70% (or more)" sequence identity, the claims are not so limited. Accordingly, the parameters to be followed by a skilled artisan to determine "functional equivalence" are not circumscribed by either the specification or the claims. Additionally, the term "mimetic" and "analog" is not defined by the specification and the degree of structure and/or functional properties that constitute an "amino acid mimetic(analogue)" (relative to a given standard amino acid) is not defined nor is the means and conditions of measurement.

Further, the term "substantially the same amino acid sequence" is a relative term which renders the claim indefinite since this term is not precisely defined by the claim, nor does the specification provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Accordingly, the term "butyrlcholinesterase variant" is equally "relative" and indefinite. Even specifying that the "variant" possess "a 15-fold increase in hydrolysis activity" does not render claim 1 definite for the following reasons. First, the definition of "butylcholinesterase" encompasses any native mammalian butylcholinesterase and "isotype variation, polymorphism or any other allelic variation(s)

" thereof . Accordingly, there is NO specific butylcholinesterase standard for measuring increased hydrolysis activity. Secondly, specifying hydrolysis activity does not address the structural lack of metes and bounds regarding the term "variant" as discussed above.

Discussion

Applicant's arguments directed to the above indefinite rejection were considered but deemed nonpersuasive for the following reasons.

Regarding the term "butyrcholinesterase variant" applicant argues that "they are entitled to define the claim terms", and, further, that the claims are to be read and interpreted in light of the specification according to the controlling federal court decisions cited above.

Applicant's argument was considered but deemed nonpersuasive, since although applicant's entitled to define the claim terms, the claimed invention, when interpreted in light of the specification and prevailing case law must sufficiently apprise one of ordinary skill in the art what would infringe and not infringe the presently claimed invention. In this regard, as pointed out in the rejection above, the claims, when interpreted in light of the specification in accordance with prevailing law fails to define the metes and bounds in a precise manner as to what protein structure would infringe, and more importantly what protein structure would not infringe the presently claimed invention. This is true since the definitional terms of what constitutes a butyrlcholinesterase variant are imprecise and ill-defined as discussed in the rejection above (e.g. hydrolase activity less than equal to or more than; no parameters to

determine functional equivalence; may have a degree of identity; comprise "mimics", "analogs" etc which is relative terminology with no means of determination of the requisite mimicry or analogy). Applicant's arguments fail to address any of the substance of the above rejection; and accordingly, the above rejection is hereby maintained.

Turning to the term "substantially the same amino acid sequence" applicant argues that the definition of such a term as presented in pages 9-10 of the specification is definite.

This argument was considered but deemed nonpersuasive for the reasons referred to in the above rejection and for the following reasons.

The specification definition on page 9 merely requires that the claim variants comprise those variants with a sequence identical to SEQ ID 2 and additionally nonidentical sequences which are determined by one of ordinary skill in the art to be functionally equivalent. Applicant's arguments regarding degree of sequence identity (e.g. at least 70% identity) is not mandated by the specification definition, but is merely optional (e.g. "**can have** at least 70%). Accordingly, the claims, when interpreted in light of the specification in accordance with prevailing law fails to define the metes and bounds in a precise manner as to what protein structure would infringe, and more importantly what protein structure would not infringe the presently claimed invention. This is true since the definitional terms of what constitutes substantially the same amino acid sequence shown as seq. id 2, with regard to nonidentical sequences lacks sufficient metes and bounds.

Accordingly, the above indefinite rejection is hereby maintained.

New Objection (s) and/or Rejection (s)

Claim Rejections - 35 USC § 112

Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In newly amended claims 1 and 2, "A butylcholine esterase variant ... substantially the same ... as SEQ ID 2 ... has a Trptophane at amino acid position 328" is indefinite when read in light of the specification (e.g. page 22, lines 17-22 referred to by applicant) since there is NOT a tryptophan residue at position 328 of either SEQ. ID 2 or SEQ ID 17 as referred to on specification page 22 nor does the claim provide either a frame of reference or means of reconciling the amino acid numbering of either sequence to reconcile amino acid positioning as to obtain either sequence to have a Trp at "position 328".

Double Patenting

Claims 1 and 2 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33 (especially claims 1-2) of copending Application No. 10/032,233 as shown by PG PUB US 2003/0153062 (Aug. 14, 2003). The Application claims butyrcholinesterase variant peptides including seq. id 2 which contain a tryp at position 328 which inherenty

contains the presently recited biological activity (E.g. 15 fold increase in cocaine hydrolysis). It is noted that neither the 10/032,233 application nor its PG Publication were available to the Examiner at the time of the first office action.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 703-305-7556. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 703-306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
November 6, 2003